PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	A randomised controlled trial of online continuing education for health professionals to improve the management of chronic fatigue syndrome: A study protocol.
AUTHORS	Li, Sophie; Sandler, Carolina; Casson, Sally; Cassar, Joanne; Bogg, Tina; Lloyd, Andrew; Barry, Benjamin

VERSION 1 - REVIEW

REVIEWER	Robyn Fary Curtin University Australia
REVIEW RETURNED	22-Sep-2016

GENERAL COMMENTS	This is a well written and necessary study. Unfortunately there are a few inconsistencies within the protocol, in particular with reference to the cohort study component, that may make interpreting data difficult. **Abstract** No mention of follow up cohort (retention) component of the study **Introduction** Page 4 Lines 53-60 – I'm not convinced that the statement about traditional exercise programs is factually correct. A "traditional" exercise program should definitely not be continued (without any consideration) in the presence of increasing symptoms. I do not agree that the term "graded exercise therapy" (GET) is a misleading term as it is indeed "graded" to the patient. Page 5 Lines 3-17 – Description of GET needs referencing Page 5 Lines 20-32 – References to support the contention or at least acknowledge that this is anecdotal evidence. **Methods and analysis** Page 6 Lines 22 -31 – I would have thought that the plan would have been to report the study according to CONSORT guidelines and to develop the protocol in line with SPIRIT, not the other way around. Trial design does not mention the cohort study component. General question – Are data describing participant characteristics

	being collected? Not mentioned Page 9 Lines 33-35 – Data collection at three time points is mentioned. What about immediately after the wait-list control group has had access to intervention? This is necessary to continue through the cohort study where you combine all participants into one group. Consequently, there should be three time points for those who enter the intervention directly and four time points for those who are wait-listed. Pages 9 - 10 Primary outcome measures – Measurement properties of the outcome measures? Page 10 Lines 47-56 – In the absence of these data being collected at baseline, it is difficult to see what the measure of success will provide. Page 11 – Lines 3-10 – Again, if the proportion of clinical practice devoted to people with chronic fatigue syndrome is not collected at baseline I am not sure what collecting this percentage will add. Page 11 – Lines 15-20 – Follow up data measured "across the follow up period subsequent to post-intervention assessment." A follow up data collection point for the waitlist control is not reported on page 9 nor in Figure 1. General question – How are adherence/learning analytics being reported? – not mentioned in analysis section Page 12 – Line 12 – What measures of practice behaviour are being reported here? I am not sure if this is referring to changes in the proportion of people with chronic fatigue syndrome being treated or if it refers to responses to clinical vignette questions. **Discussion** Page 12 – Lines 50-55 – Learning analytics within the intervention are mentioned. These are not mentioned in the analysis. **Table 1.** Page 8 Line 25 - It would be preferable to cite a number of systematic reviews as suggested by the plural "reviews" than to use (e.g., [14]). Page 9 – Line 12 – Is this meant to be 4- weeks? If not, having the link available for 4 months is likely to confound the retention component of the study **Figure 1** Page 18 - Line 37– There is no post-intervention assessment for the wait-list control group mentioned. **Very few typographical and formatting errors**

	Page 4 – Line 19 (and there are other examples similar to this) – It is usual convention to mention that systematic reviews are being cited rather than placing the instructions “for a review see..” Page 6 – Line 3 – replace on with of Page 6 – Line 5 – replace regarding with on Page 6 – Line 22 – Only capitalise C in Consolidated Page 6 – Line 45 – Perhaps use the English version of practising Page 11 – Line 3 – Add apostrophe after Participants Page 13 – Line 12 – correct spelling of amenable **References** Inconsistent use of capital letters in journal names. References 4, 8, 14 and 15 Absence of author initials in reference 22.

REVIEWER	Dr. Keith J Geraghty University of Manchester – UK
REVIEW RETURNED	22-Nov-2016

GENERAL COMMENTS	Thank you for the opportunity to review this protocol “A randomised controlled trial of online continuing education for health professionals to improve the management of chronic fatigue syndrome. A study protocol”. I must declare a strong personal interest in this field and while this is the first ever trial protocol I have reviewed, it is not the first paper in ME/CFS. This illness is at the top of my research focus, thus I feel uniquely qualified to review this protocol. It is also a privilege to offer my review, I hope I can offer the authors some useful feedback on their trial protocol as it is presented in their paper. Abstract & Introduction The evidence that CBT may be of benefit to patients with ME/CFS is highly contested e.g. the largest ever RCT by PACE team (Lancet, 2011) and follow-up, shows that the benefits are not universal, i.e. a percentage of patients with mild to moderate ME/CFS may be helped with CBT, but the majority will not and long term benefits are inconsistent to non-existent; in addition the evidence from PACE is now highly contested and the US Agency for Health Care Research and Quality (AHRQ has down-graded its rating of CBT as an effective treatment for ME/CFS. The authors need to be careful with a blanket statement that the evidence for benefit has been shown – please add the necessary disclosures of magnitude of benefit to give the reader a realistic perspective of the meaning behind the word ‘benefit’ and show some neutrality to whether or not CBT may be of benefit. Assumed benefit may be a bias, particularly without any qualification of meaning. The authors suggest that the poor uptake of CBT is due to delayed

	diagnosis and poor availability of CBT, however it may also be due to some primary care physicians not viewing it as necessary. UK NICE guidelines only recommend GPs consider it or offer it as a treatment, the physician holds autonomy to decide if it's worth offering and where or when it is not. Your abstract assumes it is beneficial and GPs are just not aware of CBT – without considering any other explanation. Price et al. (2008) stated they found low to inconsistent evidence for CBT improving physical function over the long term – this finding has been made by others. Reviews by Kindlon (2011) and Maes and Twisk (2009) and Twisk and Geraghty (2015) report significant harms in ME/CFS who undergo CBT and GET – you only report positive RCT evidence and make no mention of these papers (giving a one-sided view of efficacy and benefit is not an impartial position and should be rectified by offering the reader a fair assessment of the literature – I direct you to Geraghty and Blease (2016) Journal of Health Psychology "the efficacy of CBT" – this paper offers an alternative view of benefit. There is a large body of survey evidence from ME/CFS patient groups that suggest CBT and GET are ineffective – patient experience evidence is valuable and worth including – See for example reports by Action for ME UK surveys or the ME Association (MEA) 2015 patient survey on CBT/GET and Pacing. The MEA call the NICE guidelines that recommend CBT and GET "not fit for purpose" – so this hardly compares to the authors' statement in introduction that CBT is beneficial and just not advertised well enough to health professionals. Page 5: 39 – if you look at Geraghty and Blease 2016 "consent in CBT" – you will see that its doctors prescribe CBT to patients and refer them to CBT clinics, whereby either psychiatrist, psychologist or CBT practitioner will usually offer CBT – I am not sure about the authors statement that 'all allied health professionals need to have a capacity to offer CBT/GET' – one can see poor logic here. Please qualify your statements. P5. L40 – rights about access to treatments is a complex socio-political and ethical area of medicine – I point you again to Geraghty and Blease (2016), patients have many rights, including the right to full disclosure of the efficacy of CBT – the authors seem to fail the tenets of this paper by wanting to offer CBT on the proviso "it works" – without any disclosure of how, why, for whom, under what circumstances, and to also disclose risks and alternatives to patients/ and in this case, practitioners. P6. L50 – the authors admit that the term "graded exercise therapy" is a misleading name, given it is taken to mean 'increasing activity' – yet then argue, it's actually more about Pacing then trying to increase activity – and I assume it also means going back to Pacing if over-activity induces post-exertional malaise – do you not think it wise to change the name to something more appropriate, if it's so misleading? Like "Pacing and activity advice"? You even say it's not to be seen as a traditional 'exercise programme' thus shouldn't the word exercise be removed? P6. L3 – You state "The aim of this trial is to evaluate the effect of participation in an online education program, compared with a wait-list control group, on allied health practitioners' knowledge about evidence-based CFS interventions and their levels of confidence to deliver these interventions." – I find the term 'wait-list group' slightly confusing, usually patients are in the waiting list, not the practitioners offering treatments? P6. L37 – we get to see who you mean by Allied health professionals here: Australian allied health practitioners (e.g., Psychologists, Exercise Physiologists, Physiotherapists,

	Occupational Therapists). There is a concern here, that exercise professionals e.g. physios and OTs may not be appropriately trained to offer CBT and vice versa, psychologists may not be trained how to offer exercise therapies, so I have grave concerns for patients being treated by allied health professionals that lack expert knowledge of these treatments - a world of risks or harm and lack of competencies opens up here. P6. In advertising for physios and OTs and so on – what will the adverts ask them to contact you for, will it be to take part in training for CBT and GET for ME/CFS? One has to consider the self-selection bias here so it's important we know why the participants are joining the study. There are many biases that creep into the design phase of trials – like training therapists to perceive that CBT is a 'very' effective treatment for CFS/ME – then asking them if they perceive it to be 'effective' for example. Please keep this in mind. P7. L40 – I would like to review the actual intervention if possible? It's hard for me to review an education program that I haven't seen, you give an overview map of the program but not the actual full online version. P9-10 Primary outcomes measures 1. Participants' knowledge about CFS and CFS interventions measured at post intervention compared with baseline. (Multiple choice and short answer questions, integrated with case vignettes, will test participants' knowledge about CFS symptoms, differential diagnosis, CFS management strategies and interventions (CBT and GET), and interventions for conditions that commonly arise secondary to fatigue (reduced mood and anxiety). **** here I worry are you asking physios and OTs to have knowledge of how to assess a patient with CFS for secondary depression, anxiety and other mental health conditions? – based on a 4 week online course? The word diagnosis needs to be removed – this is the responsibility of a primary physician or specialist who refers the patient for treatment, and trained and registered psychologists may use their expertise to diagnose depression but a physio or OT should not be asked to do this, esp. On the back of a 4-week online education programme about CFS. 2. Participants self-reported confidence in their knowledge of CFS and confidence in their clinical skills to implement evidence-based CFS interventions. This part of the questionnaire requires participants to rate their confidence in their knowledge and clinical skills related to CFS using a 5-point Likert scale anchored at one end with "not at all confident" and at the other end "very confident". *I assume the other points are "not very confident", "somewhat confident" and "confident" ? P10 L19 Secondary outcome measures You sort of give the game away that this is not really a randomised controlled trial – in the secondary outcomes measures you are only looking at the group given the education programme, because the other group is really given nothing, or at least nothing until they do get the education programme in week 5 after baseline assessments have been completed. If any of these allied health professionals are friends or colleagues and one group are doing the education programme and their friend is not, any communication between the two will generate negative responses in the non-ed program group. Indeed, can we really call this an RCT when we have one group of

	allied professionals being given an ed program and the other group are given nothing (and by nothing we don't mean a blinded placebo sugar pill, we mean nothing) thus there is no control or comparison group here --- the authors have artificially generated the notion of an RCT, most likely driven by the culture in academia to perceive RCTs to be superior and evidence from RCTs to hold more weight, we see the authors quote Level 1 evidence (the notion of a level of evidence above another level of evidence is rather subjective and contested). RCTs properly conducted in appropriate settings are very valuable, but I feel the authors of this trial have pushed the meaning of RCT to its limit – this really isn't an RCT, I would therefore urge the authors to present it as a cohort study of some kind – e.g. an education program study. The idea of an RCT is to limit biases – but there are so many in this study that one could hardly hang on to the term RCT. See for example Sibbald and Roland (1998) BMJ article on what RCTs are – and ask if your RCT meets all of these requirements – I would argue not. The secondary outcome is simply how well the participants stuck to the program – how can we evaluate this for the control group, when they weren't given the program? The control is given nothing, so what are we evaluating, how well an education program helped one group perceive CFS and their attitudes to CFS versus another group who received nothing? This is why the term RCT is inappropriate. P10 L41 Cohort study outcomes I have a problem with the 'Primary outcome measures' here. You wish to assess participants' self-reported success in treating people with CFS or medically-unexplained fatigue. First I will jump in and say you have now included a second group of patients in the study, not listed above or in the title, you are now saying you are assessing participants views of success at treating patients with medically unexplained fatigue – this could also be written as medically unexplained symptoms (fatigue is ubiquitous to many illness states). You have strayed across to another group of patients with MUS (medially unexplained symptoms). Please remove. For those with CFS/ME, am I right in assuming they are self-referred to the allied health professionals who see them, or are the allied health professionals who see them recounting that they have seen patients with CFS/ME – if the latter there is considerable risk of bias, recall and other, mis-diagnosis and so on – this is a problem I flagged above in terms of the problem and difficulty in making an accurate diagnosis of CFS/ME and the risk of asking non-specialist allied professionals to take this on – there is also a large legal risk here of medical negligence. P11 L3 Same as above – I am particularly confused by asking participants what percentage of time they devote to ME/CFS or MUS? What is the purpose of this evaluation? For example, if you train the intervention arm to be more aware of ME/CFS and MUS are you not biasing any follow-on question to see what percentage of time they devote to ME/CFS/MUS – if its raised you may think the intervention has had a positive impact – it may simply be the bias you have designed into the study and even if they do report devoting more time – what does this tell us? Much of this is not explained. • We must remember you are proposing to give the control arm the same programme at a different time – hence same issues as above. I am also confused by RCT main primary and secondary measures and then an added in cohort evaluation of primary and secondary measures that overlap greatly – these need to be justified rather than just thrown into the mix, i.e. what was the rationale for these

	measures? What was the rationale for main study measures versus in-cohort measures? Perhaps the rationale could be made clearer. P12 L31-32 Discussion You again return to the notion that there has been a limited uptake of CBT and GET for the management of ME/CFS – here no mention of MUS. Again, you suggest indirectly that CBT-GET are beneficial at "improving patient function", you really need to clarify this statement, the evidence I am aware of shows that CBT and GET has little impact on restoring physical function in ME//CFS over the long term (see Price et al., 2008 or even the PACE trial follow-up paper Sharpe et al., 2012). You almost assume things without explanation. P12-40 You mention 'clinicians' here and 'allied health professionals' suggesting there is no research on educational programmes for clinicians – I must point out your RCT is aimed only at allied health professionals and not medical practitioners, thus you need to make this clear in these statements, as you lump the two together. P13 "future further" – only on word to mean the same thing – My summary conclusions: Many aspects of this trial have not been fully considered. What jumps off the pages is that the trial team assume and accept that CBT and GET are beneficial and they are going to disseminate this notion to allied health professionals via an online education programme and then assess the impact of this programme on allied professions (OTs physios and so on) attitudes towards using these practices when dealing with ME/CFS patients. Secondly, the overarching bias of the assumed benefit of CBT and GET hangs over this trial. The authors should be taking a neutral stance, yet appear to be highly impartial. There are no questions from what I see, to assess the feedback patients offer the allied health professionals that apply the education programme in clinical practice? Thirdly, I understand that there is pressure to produce robust evidence that stands above others and that randomised controlled trials might be considered 'level 1 evidence' – I am rather more sceptical, however it appears that authors have framed this study around an RCT, yet this trial fails to resemble an RCT across many areas – for example, there is no blinding (other than partial blinding of data assessors), no adequate control group, the time frame for assessments is very short and the premise of the education programme is to educate allied health professionals of the benefits of CBT and GET for CFS, thus this could hardly be described as an RCT of a treatment or intervention to two groups each blinded to the intervention, with a strong emphasis on minimised the risk of bias, placebo and trial contamination. I would recommend changing the study design format to something more fitting – such as a study of an education intervention with a survey method. References: Price et al I have it as 2008 not 2009 as you have – do you have a different version ? Cochrane Database Syst Rev. 2008 Jul 16;(3):CD001027. doi: 10.1002/14651858.CD001027.pub2. Or Price JR1, Mitchell E, Tidy E, Hunot V. Cochrane Database Syst Rev. 2008 Jul 16; (3):CD001027. doi: 10.1002/14651858.CD001027.pub2. Cognitive behaviour therapy for

	chronic fatigue syndrome in adults. Sharpe, Michael et al. (2015) Rehabilitative treatments for chronic fatigue syndrome: long-term follow-up from the PACE trial The Lancet Psychiatry , Volume 2 , Issue 12 , 1067 – 1074. Sibbald, B and Roland, M (1998) Understanding controlled trials: Why are randomised controlled trials important? BMJ 1998;316:201 Smith ME, Haney E, McDonagh M, Pappas M, Daeges M, Wasson N, et al. Treatment of Myalgic Encephalomyelitis/chronic fatigue syndrome: A systematic review for a National Institutes of Health pathways to prevention workshop. Ann Intern Med. 2015 Jun 16; 162(12):841-850. doi: 10.7326/M15-0114. Twisk FNM, Maes M. A review on cognitive behavorial therapy (CBT) and graded exercise therapy (GET) in myalgic encephalomyelitis (ME) / chronic fatigue syndrome (CFS): CBT/GET is not only ineffective and not evidence-based, but also potentially harmful for many patients. Neuro Endocrinol Lett. 2009; 30(3):284-299. PMID: 19855350. PMID: 19855350. Twisk, F. and Geraghty, K. (2015) Deviant Cellular and Physiological Responses to Exercise in Myalgic Encephalomyelitis and Chronic Fatigue Syndrome, Jacobs Journal of Physiology, 1(2), 007, 2015. Van Dessel N, den Boeft M, van der Wouden JC, Kleinstäuber M, Leone SS, Terluin B, et al. Non-pharmacological interventions for somatoform disorders and medically unexplained physical symptoms (MUPS) in adults. Cochrane Database Syst Rev. 2014 Nov 1;(11):CD011142. PMID: 25362239. doi: 10.1002/14651858.CD011142.pub2

REVIEWER	Martine M. Goedendorp Department of Health Psychology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
REVIEW RETURNED	28-Nov-2016

GENERAL COMMENTS	Thank you for giving me the opportunity to review this study protocol about education of health professionals on management of CFS. It is clearly written manuscript and a relevant study for clinical practice. There are several aspect missing in the study protocol that could influence the quality of the to be performed RCT. Introduction Education about CFS is the topic of this manuscript, but I miss the used definition of CFS. In the intervention description the authors mention chronic fatigue states. In the outcome measure they distinguish CFS from medically unexplained fatigue, but they do not explain this difference, and why they used this difference. In the new DSM 5 the definition somatic symptom disorder changed. A key change in the DSM-5 criteria is that while medically unexplained symptoms were a key feature for many of the disorders in DSM-IV, an SSD diagnosis does not require that the somatic symptoms are medically unexplained. (http://www.dsm5.org/documents/somatic%20symptom%20disorder

	%20fact%20sheet.pdf). It would be of added value to include a definition of CFS and use this definition throughout the whole study. The authors describe that uptake of CFS management programs is low, because health profession lack the knowledge and skill to provide appropriate care. However, the authors do not describe which health professionals are involved in the care for CFS patients. Based on the recruitment I assume that physical therapists and psychologists are their target population, but this is not clearly described. Are GPs, or other clinicians referring patients, not approached in this study? In the introduction the authors describe the difference between traditional exercise programs and GET for CFS, however they do not explain the difference between GET and pacing. I think that would be of added value as the evidence for pacing as an effective intervention is not strong. White, P. D., Goldsmith, K. A., Johnson, A. L., Potts, L., Walwyn, R., DeCesare, J. C., et al. (2011). Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet (London, England), 377(9768), 823-836. In the introduction only the primary aim is explained, while the secondary aims are not explained. Methods In the methods the RCT is described briefly, but the cohort study is not. I read about the cohort study in the paragraph about outcomes. It should be described earlier in the manuscript. In the recruitment procedure it is briefly described that health practitioners will be recruited via advertisements, but it is unclear what happens next. Do participants need to sign up somewhere? I assume they will be in contact with an investigator before consenting to participate, and gaining access to the education program. This should be described. The block sizes of 2-6 seem to be small, specifically 2. This might be a risk for bias. The person performing the randomization might not be blind for the allocation. In the methods it is described that the link to the study is available for 4 months, however the post-intervention assessment will be after 4-5 weeks, and the follow-up assessment after 12 weeks. Does this mean that the intervention group might not be finished with the intervention, and that the post-intervention assessment is not really a post-intervention assessment? Several aspects are not described in the methods. • Who will analyze the data, is this person blind for the group allocation? • What is the risk for contamination? • How is the privacy of participants guaranteed? • Are the outcome measures newly formed questionnaires, or based on validated questionnaires? If the questionnaires are new the validity of the questionnaire can be a serious issue.

	Discussion The fact that convenience sampling will be used in the study can be a serious threat for further implementation of this intervention. Professionals with an interest in CFS probably will sign up for this intervention, but not professionals who are skeptical towards this group of patients and the diagnosis CFS. This should be acknowledged in the discussion. The discussion starts with “the limited understanding of the pathophysiological mechanisms and absence of curative treatments”, while the introduction starts with the benefits of CBT and GET. The authors seem to bring up a new issue here, while it is not previously described. I think the main issue is the limited uptake of CFS management programs, and limited knowledge of health professionals, and that this should be the main issue that the researches will try to improve.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Robyn Fary
Institution and Country: Curtin University, Australia
Please state any competing interests or state ‘None declared’: None declared

This is a well written and necessary study. Unfortunately there are a few inconsistencies within the protocol, in particular with reference to the cohort study component, that may make interpreting data difficult.

Abstract
No mention of follow up cohort (retention) component of the study
RESPONSE: Description of the cohort study has been added to the Methods and Analysis section of the abstract: Retention of knowledge, satisfaction with the online education program and the influence of the education program on clinical practice behaviour will also be assessed in a cohort study design with participants pooled from the intervention and wait-list control groups. (p.2, line 22-23).

Introduction
Page 4 Lines 53-60 – I’m not convinced that the statement about traditional exercise programs is factually correct. A “traditional” exercise program should definitely not be continued (without any consideration) in the presence of increasing symptoms. I do not agree that the term “graded exercise therapy” (GET) is a misleading term as it is indeed “graded” to the patient.
RESPONSE: It has been our substantial clinical experience that some clinicians and patients do perceive “GET” to imply a traditional exercise program and may therefore disregard symptom exacerbation and encourage patients to “soldier on”. We acknowledge that some clinicians appropriately grasp the intended meaning of “graded exercise therapy”. We have revised the sentence: “(this is an easy mistake to make given the potentially misleading term: graded exercise therapy).” (p. 5, line 6).

Page 5 Lines 3-17 – Description of GET needs referencing
RESPONSE: Reference [7], (Sandler CX, Hamilton B, Horsfield S, Bennett B,Vollmer-Conna U, Tzarimas C, Lloyd AR. Outcomes and predictors of response from an optimised, multi-disciplinary intervention for chronic fatigue states. Internal Medicine Journal in press doi: 10.1111/imj.13251), has

been added to provide a reference for the definition of GET. (p.5, line 15).

Page 5 Lines 20-32 – References to support the contention or at least acknowledge that this is anecdotal evidence.
RESPONSE: The following text and references have been added to support the efficacy of online education for improving health professional knowledge and practice: “An alternative method to improve health professional knowledge and practice is through online education programs, as has been demonstrated in other areas of health care (for example, [22, 23]).” (p. 6, line 12-13)
References:
22. Fary RE, Slater H, Chua J, Ranelli S, Chan M, Briggs AM. Policy-into-practice for rheumatoid arthritis: randomized controlled trial and cohort study of e-learning targeting improved physiotherapy management. Arthritis care & research 2015;67(7):913-22 doi: 10.1002/acr.22535[published Online First: Epub Date]|.
23. Harvey LA, Glinsky JV, Lowe R, Lowe T. A massive open online course for teaching physiotherapy students and physiotherapists about spinal cord injuries. Spinal cord 2014;52(12):911-8 doi: 10.1038/sc.2014.174[published Online First: Epub Date]|.

Methods and analysis
Page 6 Lines 22 -31 – I would have thought that the plan would have been to report the study according to CONSORT guidelines and to develop the protocol in line with SPIRIT, not the other way around. Trial design does not mention the cohort study component.
RESPONSE: The BMJ Open author guidelines require reporting of protocols according to the SPIRIT statement. The completed study will be reported according to CONSORT guidelines. To improve clarity regarding the guidelines used to develop and report the protocol the text has been revised to: “The trial design was developed and is reported according to the Recommendations for Interventional Trials (SPIRIT) statement (24) and the education intervention is described according to the Template for Intervention Description and Replication (TIDieR) checklist (27)”. (p. 7, line 2-5).

Thank you for noting the omission of the cohort study in the description of the trial design. The cohort study has been mentioned with the following text added: “In addition to the RCT, a cohort study will be conducted that will assess changes in self-reported success in treating people with CFS and practice behaviours from baseline to follow-up for both groups combined.” (p. 7, line 5-8).

General question – Are data describing participant characteristics being collected? Not mentioned
RESPONSE: Thank you for noting this omission. The following text has been added under Outcomes: “In addition, information regarding profession type of the individual and years of practice will be collected to determine profession and level of professional experience.” (p. 11, line 5-6).

Page 9 Lines 33-35 – Data collection at three time points is mentioned. What about immediately after the wait-list control group has had access to intervention? This is necessary to continue through the cohort study where you combine all participants into one group. Consequently, there should be three time points for those who enter the intervention directly and four time points for those who are wait-listed.
RESPONSE: We apologise for the lack of clarity provided in the manuscript regarding the assessment of retention of knowledge. In designing the study, we made a pragmatic decision to exclude an assessment immediately after access to the online education activity for the wait-list control group because our belief was that requiring the completion of an additional assessment by the control group would result in high dropout rates. The obvious disadvantage of this design is that we are only able to assess retention of knowledge in the Education group. The advantage, however, is that we are able to analyse the Follow-up assessment results for the entire cohort to determine change in practice behaviours and perceived success in treating people with CFS from baseline to

follow-up.

To improve clarity regarding the design of the study, we have moved the secondary outcome measure of knowledge/confidence retention to under the RCT study secondary outcome measures heading. (p. 12, line 1-3).

Pages 9 - 10 Primary outcome measures – Measurement properties of the outcome measures?
We acknowledge that these measures have not yet been through a validation process. The content of the outcome measures has been constructed by an expert research group consisting of physicians, exercise physiologists and clinical psychologists and designed to test a range of knowledge across different professions.

The following text has been added to acknowledge this lack of validation: “These measures have been constructed by an expert research group consisting of physicians, exercise physiologists and clinical psychologists and designed to test knowledge across the range of allied health professions.” (p. 11, line 20-22)

Page 10 Lines 47-56 – In the absence of these data being collected at baseline, it is difficult to see what the measure of success will provide.
RESPONSE: These data are collected at all three assessment time points as specified in the first sentence under the Outcomes heading. To clarify the outcome measure collection time points the following text has been added:
1. All outcomes (with the exception of adherence to and satisfaction with the online education activity) will be determined by participants completing an online questionnaire and assessment at three time points. (p. 10, line 7-8)
2. Under the cohort study outcomes heading: “Primary outcome measures are assessed at baseline and follow-up, and are:” (p. 12, line 14)

Page 11 – Lines 3-10 – Again, if the proportion of clinical practice devoted to people with chronic fatigue syndrome is not collected at baseline I am not sure what collecting this percentage will add.
RESPONSE: See response to previous comment.

Page 11 – Lines 15-20 – Follow up data measured “across the follow up period subsequent to post-intervention assessment.” A follow up data collection point for the waitlist control is not reported on page 9 nor in Figure 1.
RESPONSE: Under the heading Outcomes, the following text states the data collection time points for the wait-list control group: “while the follow-up measures will be completed in week 12 for the education group and week 16 for the wait-list control group, which for both groups is eight weeks after cessation of access to the online education.”. To improve clarity, we have added the text: “while the follow-up measures will be completed in week 12 for the education group and week 16 for the Control group (i.e, 8 weeks after cessation of access to the online education for both groups)”. (p. 11, line 1-2)

General question – How are adherence/learning analytics being reported? – not mentioned in analysis section
RESPONSE: Thank you for highlighting this omission. The following text has been added: “Similarly, descriptive statistics will be generated for the total time spent on the online education program, time spent on each module, total time spent on the integrated formative assessment tasks, and responses on these tasks for each professional group.” (p. 13, line 13-16)

Page 12 – Line 12 – What measures of practice behaviour are being reported here? I am not sure if this is referring to changes in the proportion of people with chronic fatigue syndrome being treated or if it refers to responses to clinical vignette questions.

RESPONSE: To clarify that “practice behavior” refers to the proportion of people with CFS being seen in clinical practice the following text has been added: “(i.e., proportion of clinical practice devoted to the management of people with CFS)” (p. 13, line 23-24)

Discussion
Page 12 – Lines 50-55 – Learning analytics within the intervention are mentioned. These are not mentioned in the analysis.
RESPONSE: Reporting of learning analytics has now been added to the Analysis section. See previous response. (p. 13, line 13-16)

Table 1.
Page 8 Line 25 - It would be preferable to cite a number of systematic reviews as suggested by the plural “reviews” than to use (e.g., [14]).
RESPONSE: This sentence has been reworded to reference the review that has been cited: “Additionally, a large review of internet-based education programs indicates online education interventions are as effective as traditional training methods and have the advantage of being easily accessible[19].” (p. 9, table)

Page 9 – Line 12 – Is this meant to be 4- weeks? If not, having the link available for 4 months is likely to confound the retention component of the study
RESPONSE: We apologise for this typographical error and thank you for identifying it. The sentence has been corrected: “Each participant will have access to the online education program for a duration of four weeks.” (p. 10, table)

Figure 1
Page 18 - Line 37– There is no post-intervention assessment for the wait-list control group mentioned.
RESPONSE: The wait-list control group is not required to complete an assessment upon completion of the online education program. See previous responses.

Very few typographical and formatting errors
Page 4 – Line 19 (and there are other examples similar to this) – It is usual convention to mention that systematic reviews are being cited rather than placing the instructions “for a review see..” –
RESPONSE: We do not consider any change necessary here, but are happy to make changes if the editor wishes us to do so to align with BMJ Open style.

Page 6 – Line 3 – replace ‘on’ with ‘of’
RESPONSE: We have revised the original sentence so it now reads: “The aim of this trial is to evaluate the effect of participation in an online education program on allied health practitioners’ knowledge about evidence-based CFS interventions and their levels of confidence to deliver these interventions, compared with a wait-list control group.” (p. 6, line 12-13)

Page 6 – Line 5 – replace ‘regarding’ with ‘on’
RESPONSE: We cannot identify the word “regarding” in this location

Page 6 – Line 22 – Only capitalise C in Consolidated
RESPONSE: corrected as suggested

Page 6 – Line 45 – Perhaps use the English version of practicing
RESPONSE: corrected as suggested

Page 11 – Line 3 – Add apostrophe after Participants
RESPONSE: corrected as suggested

Page 13 – Line 12 – correct spelling of amenable
RESPONSE: corrected as suggested

References
Inconsistent use of capital letters in journal names. References 4, 8, 14 and 15
Absence of author initials in reference 22.
RESPONSE: corrected as suggested

Reviewer: 2
Reviewer Name: Dr. Keith J Geraghty
Institution and Country: University of Manchester – UK
Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below
Thank you for the opportunity to review this protocol "A randomised controlled trial of online continuing education for health professionals to improve the management of chronic fatigue syndrome. A study protocol". I must declare a strong personal interest in this field and while this is the first ever trial protocol I have reviewed, it is not the first paper in ME/CFS. This illness is at the top of my research focus, thus I feel uniquely qualified to review this protocol. It is also a privilege to offer my review, I hope I can offer the authors some useful feedback on their trial protocol as it is presented in their paper.

Abstract & Introduction
The evidence that CBT may be of benefit to patients with ME/CFS is highly contested e.g. the largest ever RCT by PACE team (Lancet, 2011) and follow-up, shows that the benefits are not universal, i.e. a percentage of patients with mild to moderate ME/CFS may be helped with CBT, but the majority will not and long term benefits are inconsistent to non-existent; in addition the evidence from PACE is now highly contested and the US Agency for Health Care Research and Quality (AHRQ has down-graded its rating of CBT as an effective treatment for ME/CFS. The authors need to be careful with a blanket statement that the evidence for benefit has been shown – please add the necessary disclosures of magnitude of benefit to give the reader a realistic perspective of the meaning behind the word 'benefit' and show some neutrality to whether or not CBT may be of benefit. Assumed benefit may be a bias, particularly without any qualification of meaning.
RESPONSE: We are aware of the controversy surrounding the PACE trial and accept that the benefits of CBT/GET are not universal. As such, we have not made any claims in the manuscript that CBT/GET is a universally beneficial intervention or a cure, and have in fact highlighted the absence of a curative treatment. We have attempted to be as objective and impartial as possible in presenting the evidence for the benefits of CBT/GET as an intervention and consequently have chosen to cite only those studies that have engaged the most rigorous controls in implementing their methodologies (e.g., RCTs and meta-analyses that have reviewed RCTs).
To neutralise perceived biases we have revised the text to (p. 4, line 7-15):
Although there is Level One evidence of the benefit of cognitive behavior therapy (CBT) and graded exercise therapy (GET) for some people with CFS, uptake of these interventions is low or at best untimely. More than 20 randomised controlled trials by independent researchers examining the effectiveness of CBT or GET across separate patient groups and in various geographical locations have found beneficial effects of these interventions for CFS in group-wise outcome analyses (for a review see[5]). There is also recent evidence that combining CBT and GET may be more effective than CBT alone[6]. When applied appropriately the interventions are not associated with harm[4-8], although the beneficial effects vary in magnitude from modest to clinically significant[3, 4]. These interventions have also proved generally effective in routine clinical practice[9].

The authors suggest that the poor uptake of CBT is due to delayed diagnosis and poor availability of CBT, however it may also be due to some primary care physicians not viewing it as necessary. UK NICE guidelines only recommend GPs consider it or offer it as a treatment, the physician holds autonomy to decide if it's worth offering and where or when it is not. Your abstract assumes it is beneficial and GPs are just not aware of CBT – without considering any other explanation.
RESPONSE: While there is documentation of a gap between research and practice (see references 10 and 11) we are unaware of any studies demonstrating poor uptake of evidence-based interventions being due to GPs not referring patients because they do not think the intervention is necessary. However, we do accept that there may be undocumented reasons for poor uptake and as such the text has been revised to: "This can be partly attributed to poor clinician awareness and knowledge of CFS and the CBT and GET interventions aimed at managing its symptoms." (p. 2, line 4)

Price et al. (2008) stated they found low to inconsistent evidence for CBT improving physical function over the long term – this finding has been made by others. Reviews by Kindlon (2011) and Maes and Twisk (2009) and Twisk and Geraghty (2015) report significant harms in ME/CFS who undergo CBT and GET – you only report positive RCT evidence and make no mention of these papers (giving a one-sided view of efficacy and benefit is not an impartial position and should be rectified by offering the reader a fair assessment of the literature – I direct you to Geraghty and Blease (2016) Journal of Health Psychology "the efficacy of CBT" – this paper offers an alternative view of benefit. There is a large body of survey evidence from ME/CFS patient groups that suggest CBT and GET are ineffective – patient experience evidence is valuable and worth including – See for example reports by Action for ME UK surveys or the ME Association (MEA) 2015 patient survey on CBT/GET and Pacing. The MEA call the NICE guidelines that recommend CBT and GET "not fit for purpose" – so this hardly compares to the authors' statement in introduction that CBT is beneficial and just not advertised well enough to health professionals.
RESPONSE: As mentioned in the previous response we have restricted our review of the literature to intervention studies, and randomised controlled trials and meta-analyses of RCTs that have undergone peer review, which provide the best possible evidence of treatment efficacy, and excluded opinion and commentary pieces, and surveys of advocacy groups. We agree that making the reader aware of alternative interpretations of the literature will allow them to come to their own conclusions regarding the benefits of CBT/GET. We recognize the polarized opinions of some UK-based ME/CFS patient groups, but do not believe this warrants inclusion in this protocol manuscript for an online health professional education evaluation. We have now included reference to a publication considering the controversy regarding the PACE trial analysis. Page 4 para 1" Recent studies have shown that gaps between research and practice are at least partially due to allied health professionals lacking the knowledge and skills to provide appropriate care[13, 14], and potentially also the effects of the controversy regarding the PACE trial analysis[15]"
Reference details:
15. Smith R. Richard Smith: QMUL and King's college should release data from the PACE trial. Secondary Richard Smith: QMUL and King's college should release data from the PACE trial. http://blogs.bmj.com/bmj/2015/12/16/richard-smith-qmul-and-kings-college-should-release-data-from-the-pace-trial/. Access: December 2016

Page 5: 39 – if you look at Geraghty and Blease 2016 "consent in CBT" – you will see that its doctors prescribe CBT to patients and refer them to CBT clinics, whereby either psychiatrist, psychologist or CBT practitioner will usually offer CBT – I am not sure about the authors statement that 'all allied health professionals need to have a capacity to offer CBT/GET' – one can see poor logic here. Please qualify your statements.
RESPONSE: In Australasia, Europe, and the USA, after suitable training CBT interventions can be provided by several different allied health professionals. We acknowledge that the expertise to

provide CBT is not always present despite its application. The goal of the online education program, therefore, is to provide allied health professionals with the knowledge to identify people presenting with CFS and provide evidence-based treatment appropriately. Part of this training is to identify when further expertise is required and when a multi-disciplinary approach is necessary. In the context of multidisciplinary treatment it is beneficial for all participating clinicians to be somewhat familiar with treatment provided by the colleagues from other health professions. The online education investigated in this study seeks to support this awareness.

P5. L40 – rights about access to treatments is a complex socio-political and ethical area of medicine – I point you again to Geraghty and Blease (2016), patients have many rights, including the right to full disclosure of the efficacy of CBT – the authors seem to fail the tenets of this paper by wanting to offer CBT on the proviso "it works" – without any disclosure of how, why, for whom, under what circumstances, and to also disclose risks and alternatives to patients/ and in this case, practitioners.
RESPONSE: As evidenced by the RCTs and meta-analyses cited in the manuscript, and as evidenced by Sandler et al (in press), for many people with CFS CBT/GET does have clinically significant benefits, and for other less so. The online education program provides links to all the references cited including specific discussion of the controversy regarding the PACE trial analysis. This is to allow the practitioner the opportunity to make his or her own decision about the efficacy of CBT/GET as an intervention. While the online education program does highlight the importance of patient rights, adherence to patient's rights is the responsibility of the individual health professional, which is not an intrinsic component of this online health professional education evaluation.

P6. L50 – the authors admit that the term "graded exercise therapy" is a misleading name, given it is taken to mean 'increasing activity' – yet then argue, it's actually more about Pacing then trying to increase activity – and I assume it also means going back to Pacing if over-activity induces post-exertional malaise – do you not think it wise to change the name to something more appropriate, if it's so misleading? Like "Pacing and activity advice"? You even say it's not to be seen as a traditional 'exercise programme' thus shouldn't the word exercise be removed?
RESPONSE: Our response to reviewer 1 addresses the confusion that may sometimes arise from the term "graded exercise therapy". We are particular to provide a clear definition of GET and have also expanded our definition of pacing in response to comments from reviewer 3. We recognize the pros and cons of the label GET, but we do not believe the renaming of GET is appropriate in this manuscript given that all of the relevant literature uses this term.

P6. L3 – You state "The aim of this trial is to evaluate the effect of participation in an online education program, compared with a wait-list control group, on allied health practitioners' knowledge about evidence-based CFS interventions and their levels of confidence to deliver these interventions." – I find the term 'wait-list group' slightly confusing, usually patients are in the waiting list, not the practitioners offering treatments?
RESPONSE: We disagree, the term wait-list control group accurately describes the study design and group.

P6. L37 – we get to see who you mean by Allied health professionals here: Australian allied health practitioners (e.g., Psychologists, Exercise Physiologists, Physiotherapists, Occupational Therapists). There is a concern here, that exercise professionals e.g. physios and OTs may not be appropriately trained to offer CBT and vice versa, psychologists may not be trained how to offer exercise therapies, so I have grave concerns for patients being treated by allied health professionals that lack expert knowledge of these treatments - a world of risks or harm and lack of competencies opens up here.
RESPONSE: The purpose of the online education program is to provide clinicians with the skills required to provide evidence-based interventions for CFS and to provide appropriate patient care. As per the previous response, knowing when to refer a patient on to someone with appropriate expertise

is part of this training, as is when it is necessary to work in a multi-disciplinary context in providing the intervention.

P6. In advertising for physios and OTs and so on – what will the adverts ask them to contact you for, will it be to take part in training for CBT and GET for ME/CFS? One has to consider the self-selection bias here so it's important we know why the participants are joining the study. There are many biases that creep into the design phase of trials – like training therapists to perceive that CBT is a 'very' effective treatment for CFS/ME – then asking them if they perceive it to be 'effective' for example. Please keep this in mind.
RESPONSE: The recruitment notices state that an RCT is being conducted to determine the effectiveness of an online education program in improving clinician knowledge and confidence in managing people with CFS. We agree that this may result in a selection bias and we will be careful to report the level of confidence, expertise and practice behaviours of the participants prior to completing the online education program (i.e., at baseline).

To acknowledge this potential sampling bias, the following has been added under the Analysis heading: "The range in proportion of clinical practice devoted to people with CFS at baseline for both groups will also be described to account for potential biases in sampling." (p. 13, line 24; p. 14, line 1-2) and in the discussion: "Given the possibility of convenience sampling of allied health professionals further investigation regarding the efficacy of the intervention on a sample that have yet to formulate opinions regarding intervention for CFS would also be valuable (e.g., implemented within a tertiary allied health training program or mandated for all staff within a health professional service)." (p. 15, line 1-4)

P7. L40 – I would like to review the actual intervention if possible? It's hard for me to review an education program that I haven't seen, you give an overview map of the program but not the actual full online version.
RESPONSE: We are grateful for the reviewer's examination of the study protocol. We look forward to presenting our formal, controlled evaluation of the intervention on completion of the proposed study.

P9-10 Primary outcomes measures

1. Participants' knowledge about CFS and CFS interventions
measured at post intervention compared with baseline. (Multiple choice and short answer questions, integrated with case vignettes, will test participants' knowledge about CFS symptoms, differential diagnosis, CFS management strategies and interventions (CBT and GET), and interventions for conditions that commonly arise secondary to fatigue (reduced mood and anxiety).

**** here I worry are you asking physios and OTs to have knowledge of how to assess a patient with CFS for secondary depression, anxiety and other mental health conditions? – based on a 4 week online course? The word diagnosis needs to be removed – this is the responsibility of a primary physician or specialist who refers the patient for treatment, and trained and registered psychologists may use their expertise to diagnose depression but a physio or OT should not be asked to do this, esp. On the back of a 4-week online education programme about CFS.
RESPONSE: The study is assessing the efficacy of the online education program to improve allied health professional knowledge and confidence to provide evidence-based interventions for CFS. This includes knowledge of, and ability to recognise, the presence of secondary mental health conditions that are common in people with CFS. Recognition of secondary conditions will allow for an appropriate intervention plan to be devised, and will allow to health professional to determine when it is appropriate to refer to other professionals with the appropriate expertise or when to work in a multi-disciplinary context. The outcome measures will therefore assess all participants' capacity to recognise the presence of secondary mental health conditions.

We believe being aware of diagnostic criteria and having the ability to determine secondary or comorbid conditions is crucial to the development of an appropriate treatment plan and successful intervention. While we would hope that people with CFS present to allied health professionals via a primary physician or specialist referral in most countries this will commonly not be the case. Assessment of diagnostic criteria will also allow the allied health professional to assess the efficacy of their treatment by assessing changes in those symptoms that make up the condition.

2. Participants self-reported confidence in their knowledge of CFS and confidence in their clinical skills to implement evidence-based CFS interventions. This part of the questionnaire requires participants to rate their confidence in their knowledge and clinical skills related to CFS using a 5-point Likert scale anchored at one end with “not at all confident” and at the other end “very confident”.

*I assume the other points are “not very confident”, “somewhat confident” and “confident” ?
RESPONSE: Each point on the Likert scale has been included. The text has been revised to: “This part of the questionnaire requires participants to rate their confidence in their knowledge and clinical skills related to CFS using a 5-point Likert scale (“not at all confident”, “not very confident”, “somewhat confident”, “confident” and “very confident”).” (p. 11, line 15-16).

P10 L19 Secondary outcome measures
You sort of give the game away that this is not really a randomised controlled trial – in the secondary outcomes measures you are only looking at the group given the education programme, because the other group is really given nothing, or at least nothing until they do get the education programme in week 5 after baseline assessments have been completed. If any of these allied health professionals are friends or colleagues and one group are doing the education programme and their friend is not, any communication between the two will generate negative responses in the non-ed program group. Indeed, can we really call this an RCT when we have one group of allied professionals being given an ed program and the other group are given nothing (and by nothing we don’t mean a blinded placebo sugar pill, we mean nothing) thus there is no control or comparison group here --- the authors have artificially generated the notion of an RCT, most likely driven by the culture in academia to perceive RCTs to be superior and evidence from RCTs to hold more weight, we see the authors quote Level 1 evidence (the notion of a level of evidence above another level of evidence is rather subjective and contested). RCTs properly conducted in appropriate settings are very valuable, but I feel the authors of this trial have pushed the meaning of RCT to its limit – this really isn’t an RCT, I would therefore urge the authors to present it as a cohort study of some kind – e.g. an education program study. The idea of an RCT is to limit biases – but there are so many in this study that one could hardly hang on to the term RCT. See for example Sibbald and Roland (1998) BMJ article on what RCTs are – and ask if your RCT meets all of these requirements – I would argue not.
The secondary outcome is simply how well the participants stuck to the program – how can we evaluate this for the control group, when they weren’t given the program? The control is given nothing, so what are we evaluating, how well an education program helped one group perceive CFS and their attitudes to CFS versus another group who received nothing? This is why the term RCT is inappropriate.
RESPONSE: The study is indeed randomized. Upon providing consent and verification of inclusion criteria participants are randomly allocated (using a computer generated randomized number sequence) to either the education or control group. Experimenters are blind to which participants are allocated to which group. Change scores in knowledge and confidence to treat from baseline to post-intervention are compared between the two groups to determine whether those that received the intervention (education group) performed better on the outcome measures compared to the control group that did not receive the intervention. Essentially, our RCT study design is answering the question: Does completion of an online education intervention have a beneficial effect over and above

the impact of simply quizzing clinicians about CFS and its management? We acknowledge that simply testing health professionals could encourage them to seek publically available information and education themselves. Our design isolates this latter possibility from the provision on the online intervention.

The retention of knowledge is analysed in the education group only because the control group are not assessed immediately after having access to the online education program, we are therefore unable to assess if what they learned from the online education program was retained.

We acknowledge there is some risk of contamination. In order to control for and reduced the impact of contamination on the outcomes, each participant has an individualized password to access the program. In addition, to control access to the program the participant must be enrolled into the program by the experimenter, and is subsequently un-enrolled when they have received 4-weeks of access. Furthermore, feedback to the assessment questions are not provided. The following text has been added to address the issue of contamination under the Intervention heading: “To reduce contamination each participant has an individual password to assess the online education program, and must be enrolled into the program by the experimenter (and are subsequently unenrolled once they have received 4-weeks access to the program). Furthermore, feedback to the outcome measures (i.e., the MCQs and case vignettes) are not provided.” (p. 9, line 8-12)

Wait-list control groups are very often used as control groups in RCTs across many health conditions, especially in intervention studies where it would be ethically remiss to exclude the control group from receiving the intervention (for example:[1-3]). While an active control group would be preferable, it is not possible to construct such an alternative control condition given our current resources, and potentially ethically unviable to exclude the control group from accessing the intervention.
(reference details:
1. Allen AR, Newby JM, Smith J, Andrews G. Internet-based cognitive behavioural therapy (iCBT) for posttraumatic stress disorder versus waitlist control: study protocol for a randomised controlled trial. Trials 2015;16:544 doi: 10.1186/s13063-015-1059-5[published Online First: Epub Date]|.
2. Ferguson RJ, McDonald BC, Rocque MA, et al. Development of CBT for chemotherapy-related cognitive change: results of a waitlist control trial. Psycho-oncology 2012;21(2):176-86 doi: 10.1002/pon.1878[published Online First: Epub Date]|.
3. Janse A, Worm-Smeitink M, Bussel-Lagarde J, Bleijenberg G, Nikolaus S, Knoop H. Testing the efficacy of web-based cognitive behavioural therapy for adult patients with chronic fatigue syndrome (CBIT): study protocol for a randomized controlled trial. BMC neurology 2015;15:137 doi: 10.1186/s12883-015-0392-3[published Online First: Epub Date]|.

As mentioned in the following text from the manuscript: “Adherence to, and satisfaction with, the education activity. This data will be collected for the Education group only.” (p. 12, line 4-5). Adherence to the online education program is assessed for the Education group only. The Control group received the online education program after the Post-intervention assessment.

P10 L41 Cohort study outcomes
I have a problem with the ‘Primary outcome measures’ here. You wish to assess participants’ self-reported success in treating people with CFS or medically-unexplained fatigue. First I will jump in and say you have now included a second group of patients in the study, not listed above or in the title, you are now saying you are assessing participants views of success at treating patients with medically unexplained fatigue – this could also be written as medically unexplained symptoms (fatigue is ubiquitous to many illness states). You have strayed across to another group of patients with MUS (medially unexplained symptoms). Please remove. For those with CFS/ME, am I right in assuming they are self-referred to the allied health professionals who see them, or are the allied health

professionals who see them recounting that they have seen patients with CFS/ME – if the latter there is considerable risk of bias, recall and other, mis-diagnosis and so on – this is a problem I flagged above in terms of the problem and difficulty in making an accurate diagnosis of CFS/ME and the risk of asking non-specialist allied professionals to take this on – there is also a large legal risk here of medical negligence.
RESPONSE: Medically unexplained fatigue has been removed. (p. 12, line 15 and throughout manuscript)
It is unclear how we can be accused of medical negligence by asking participants to simply subjectively report on how successful they believe they have been at treating people with CFS before and after the education intervention.

P11 L3 Same as above –
I am particularly confused by asking participants what percentage of time they devote to ME/CFS or MUS? What is the purpose of this evaluation? For example, if you train the intervention arm to be more aware of ME/CFS and MUS are you not biasing any follow-on question to see what percentage of time they devote to ME/CFS/MUS – if its raised you may think the intervention has had a positive impact – it may simply be the bias you have designed into the study and even if they do report devoting more time – what does this tell us? Much of this is not explained.
• We must remember you are proposing to give the control arm the same programme at a different time – hence same issues as above.
RESPONSE: Medically unexplained fatigue has been removed throughout the manuscript.

To improve clarity regarding practice behaviours and explain the rationale for this outcome measure the text has been revised to: “This part of the questionnaire requires the participant to indicate the percentage of their clinical practice that is devoted to management of people with CFS, for example the proportion of their clientele who have CFS, to determine levels of service provision.” (p. 12, line 22-23)

The rationale underlying this outcome measure is it will assist in determining if the online education program has resulted in an increase in service provision and impacted practice behaviours.

I am also confused by RCT main primary and secondary measures and then an added in cohort evaluation of primary and secondary measures that overlap greatly – these need to be justified rather than just thrown into the mix, i.e. what was the rationale for these measures? What was the rationale for main study measures versus in-cohort measures? Perhaps the rationale could be made clearer.
RESPONSE: It is difficult to address this comment as the reviewer has not specified how the outcome measures overlap. The primary outcome measures for the RCT are now designated as: 1) change in knowledge; and 2) change in self-reported confidence to deliver the treatment. The secondary outcome measures are now designated as: 1) retention of knowledge; and 2) adherence to the program and satisfaction (with the goal to improve the program using participant feedback). These do not overlap. The outcome measures for the Cohort Study are to: 1) determine changes in perceived success in treating CFS; and 2) identify changes in practice behaviours operationalized as the proportion of clinical practice devoted to people with CFS.

P12 L31-32 Discussion
You again return to the notion that there has been a limited uptake of CBT and GET for the management of ME/CFS – here no mention of MUS. Again, you suggest indirectly that CBT-GET are beneficial at “improving patient function”, you really need to clarify this statement, the evidence I am aware of shows that CBT and GET has little impact on restoring physical function in ME//CFS over the long term (see Price et al., 2008 or even the PACE trial follow-up paper Sharpe et al., 2012). You almost assume things without explanation.
RESPONSE: There is Level One evidence of the benefit of CBT/GET in improved symptom severity

and intermediate term functional benefit. We acknowledge that longer term benefits may or may not be sustained, but note that this is a secondary issue requiring further study which has no direct relevance to this protocol. The proposed study investigates the effectiveness of an education intervention to support clinicians to deliver these interventions to gain the Level One evidence-based outcomes (as above).

P12-40
You mention 'clinicians' here and 'allied health professionals' suggesting there is no research on educational programmes for clinicians – I must point out your RCT is aimed only at allied health professionals and not medical practitioners, thus you need to make this clear in these statements, as you lump the two together.
RESPONSE: We apologise for the confusion, practitioners is a term used in Australia for anyone practicing a profession. The term has been standardized to allied health professional throughout the manuscript.

P13 "future further" – only on word to mean the same thing –
RESPONSE: Thank you for identifying this typographical error. The typo has been corrected.

My summary conclusions:
Many aspects of this trial have not been fully considered. What jumps off the pages is that the trial team assume and accept that CBT and GET are beneficial and they are going to disseminate this notion to allied health professionals via an online education programme and then assess the impact of this programme on allied professions (OTs physios and so on) attitudes towards using these practices when dealing with ME/CFS patients. Secondly, the overarching bias of the assumed benefit of CBT and GET hangs over this trial. The authors should be taking a neutral stance, yet appear to be highly impartial. There are no questions from what I see, to assess the feedback patients offer the allied health professionals that apply the education programme in clinical practice? Thirdly, I understand that there is pressure to produce robust evidence that stands above others and that randomised controlled trials might be considered 'level 1 evidence' – I am rather more sceptical, however it appears that authors have framed this study around an RCT, yet this trial fails to resemble an RCT across many areas – for example, there is no blinding (other than partial blinding of data assessors), no adequate control group, the time frame for assessments is very short and the premise of the education programme is to educate allied health professionals of the benefits of CBT and GET for CFS, thus this could hardly be described as an RCT of a treatment or intervention to two groups each blinded to the intervention, with a strong emphasis on minimised the risk of bias, placebo and trial contamination. I would recommend changing the study design format to something more fitting – such as a study of an education intervention with a survey method.

References:

Price et al I have it as 2008 not 2009 as you have – do you have a different version ? Cochrane Database Syst Rev. 2008 Jul 16;(3):CD001027. doi: 10.1002/14651858.CD001027.pub2.

Or

Price JR1, Mitchell E, Tidy E, Hunot V. Cochrane Database Syst Rev. 2008 Jul 16; (3):CD001027. doi: 10.1002/14651858.CD001027.pub2. Cognitive behaviour therapy for chronic fatigue syndrome in adults.

Sharpe, Michael et al. (2015) Rehabilitative treatments for chronic fatigue syndrome: long-term follow-up from the PACE trial The Lancet Psychiatry , Volume 2 , Issue 12 , 1067 – 1074.

Sibbald, B and Roland, M (1998) Understanding controlled trials: Why are randomised controlled trials important? BMJ 1998;316:201

Smith ME, Haney E, McDonagh M, Pappas M, Daeges M, Wasson N, et al. Treatment of Myalgic Encephalomyelitis/chronic fatigue syndrome: A systematic review for a National Institutes of Health pathways to prevention workshop. Ann Intern Med. 2015 Jun 16; 162(12):841-850. doi: 10.7326/M15-0114.

Twisk FNM, Maes M. A review on cognitive behavorial therapy (CBT) and graded exercise therapy (GET) in myalgic encephalomyelitis (ME) / chronic fatigue syndrome (CFS): CBT/GET is not only ineffective and not evidence-based, but also potentially harmful for many patients. Neuro Endocrinol Lett. 2009; 30(3):284-299. PMID: 19855350. PMID: 19855350.

Twisk, F. and Geraghty, K. (2015) Deviant Cellular and Physiological Responses to Exercise in Myalgic Encephalomyelitis and Chronic Fatigue Syndrome, Jacobs Journal of Physiology, 1(2), 007, 2015.

Van Dessel N, den Boeft M, van der Wouden JC, Kleinstäuber M, Leone SS, Terluin B, et al. Non-pharmacological interventions for somatoform disorders and medically unexplained physical symptoms (MUPS) in adults. Cochrane Database Syst Rev. 2014 Nov 1;(11):CD011142. PMID: 25362239. doi: 10.1002/14651858.CD011142.pub2

Reviewer: 3
Reviewer Name: Martine M. Goedendorp
Institution and Country: Department of Health Psychology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below
Thank you for giving me the opportunity to review this study protocol about education of health professionals on management of CFS. It is clearly written manuscript and a relevant study for clinical practice. There are several aspect missing in the study protocol that could influence the quality of the to be performed RCT.

Introduction

Education about CFS is the topic of this manuscript, but I miss the used definition of CFS. In the intervention description the authors mention chronic fatigue states. In the outcome measure they distinguish CFS from medically unexplained fatigue, but they do not explain this difference, and why they used this difference. In the new DSM 5 the definition somatic symptom disorder changed. A key change in the DSM-5 criteria is that while medically unexplained symptoms were a key feature for many of the disorders in DSM-IV, an SSD diagnosis does not require that the somatic symptoms are medically unexplained.
(http://www.dsm5.org/documents/somatic%20symptom%20disorder%20fact%20sheet.pdf).
It would be of added value to include a definition of CFS and use this definition throughout the whole study.
REPONSE: A definition of CFS has been added: “Chronic fatigue syndrome (CFS) refers to the presence of persistent and severe fatigue that is accompanied by musculo-skeletal pain, neurocognitive difficulties, in addition to sleep and mood disturbances, and cannot be accounted for by a medical condition[1]” (reference details: Fukuda et al. Ann Intern Med. 1994;121(12):953-959. DOI: 10.7326/0003-4819-121-12-199412150-00009)
p. 4, line 2-4)

To ensure consistent reference to the above definition of CFS the term “medically unexplained fatigue” has been removed throughout the manuscript.

In regards to the term chronic fatigue states in the intervention description table, the education program provides a definition of post cancer fatigue. Therefore, the text has been revised to: “chronic fatigue states (e.g., post cancer fatigue)”. (p. 10, table)

The authors describe that uptake of CFS management programs is low, because health profession lack the knowledge and skill to provide appropriate care. However, the authors do not describe which health professionals are involved in the care for CFS patients. Based on the recruitment I assume that physical therapists and psychologists are their target population, but this is not clearly described. Are GPs, or other clinicians referring patients, not approached in this study?
RESPONSE: In order to specify the allied health professionals involved in the care of people with CFS the sentence has been revised to: “Yet uptake of evidence-based CFS management programs delivered by allied health professionals such as psychologists, exercise physiologists, and physiotherapists is low[4 5].” (p. 4, line 18-19)

In order to clarify the professionals that are being referred to throughout the manuscript the term “health professionals” has been revised to “allied health professionals”.

GPs, specialists and nurses are not approached in this study, however, if the outcomes of this study suggest the online education program is effective another study recruiting these professions will be run.

In the introduction the authors describe the difference between traditional exercise programs and GET for CFS, however they do not explain the difference between GET and pacing. I think that would be of added value as the evidence for pacing as an effective intervention is not strong.
White, P. D., Goldsmith, K. A., Johnson, A. L., Potts, L., Walwyn, R., DeCesare, J. C., et al. (2011). Comparison of adaptive pacing therapy, cognitive behaviour therapy, graded exercise therapy, and specialist medical care for chronic fatigue syndrome (PACE): a randomised trial. Lancet (London, England), 377(9768), 823-836.
RESPONSE: A definition of activity pacing has been added to demonstrate the difference between pacing and GET: “However, after appropriate day-to-day pacing of regular activities has been established - that is, establishing a daily or weekly schedule of activities that does not exceed the individual’s energy thresholds [7]- GET merely commences with conservative incremental increases in the duration of daily physical activities, including incidental tasks such as domestic chores. This is followed by gradual progression to more structured exercise, such as walking, which is introduced and cautiously increased in a graded fashion, generally at levels far below physical activity guidelines for the general population” (p. 5, line 9-14)

To demonstrate that there is not strong evidence for pacing alone as an intervention, the following sentence has been added to the introduction: “The implementation of GET as part of an intervention for people with CFS subsequent to the establishment of appropriate pacing of activities is important because activity pacing alone does not consistently provide benefit [7, 18]” (p. 5, line 16-18)

In the introduction only the primary aim is explained, while the secondary aims are not explained.
RESPONSE: To explain the secondary outcomes the following text has been added: “Retention of knowledge, satisfaction with the online education program and the influence of the education program on clinical practice behaviour will also be assessed, in a cohort study design with participants pooled from the intervention and control groups.” (p.6, line 17-20)

Methods

In the methods the RCT is described briefly, but the cohort study is not. I read about the cohort study in the paragraph about outcomes. It should be described earlier in the manuscript.
RESPONSE: As suggested by the reviewer, the cohort study has been mentioned in the Trial design section with the following text added: “In addition to the RCT, a cohort study will be conducted that will assess changes in self-reported success in treating people with CFS and practice behaviours from baseline to follow-up for both groups combined.” (p. 7, line 5-8)

In the recruitment procedure it is briefly described that health practitioners will be recruited via advertisements, but it is unclear what happens next. Do participants need to sign up somewhere? I assume they will be in contact with an investigator before consenting to participate, and gaining access to the education program. This should be described.
RESPONSE: To further describe the recruitment process the following text has been added: “The recruitment notices and advertisements will contain a hyperlink that when accessed will provide information about the study and allow the individual to provide consent if wishing to participate. Those consenting to participate will then be contacted by an experimenter with further instructions regarding the trial.”)p. 7, line 21-24)

The block sizes of 2-6 seem to be small, specifically 2. This might be a risk for bias. The person performing the randomization might not be blind for the allocation.
RESPONSE: Small block sizes were selected to account for the possibility that particular allied health professional groups may sign up to participate in the study in a blocked fashion, based on profession type, according to when recruitment notices are posted by their professional organisations. The block sizes are akin to those used in similar studies (e.g., [6]Tiedemann etal. BMJ open 2014;4(11):e007032 doi: 10.1136/bmjopen-2014-007032) and we should also emphasise that the size of blocks implemented within the randomization has been randomly varied from 2 – 6 to ensure that the allocation of participants cannot be predicted.

In the methods it is described that the link to the study is available for 4 months, however the post-intervention assessment will be after 4-5 weeks, and the follow-up assessment after 12 weeks. Does this mean that the intervention group might not be finished with the intervention, and that the post-intervention assessment is not really a post-intervention assessment?
RESPONSE: We apologise for this confusing typo. The participants will have access to the online education activity for 4-weeks (not months), after which they will be unenrolled from the program and unable to access it. The text in the Intervention description table has been revised to read: “Each participant will have access to the online education program for a duration of four weeks.” (p. 10, table)

Several aspects are not described in the methods.
• Who will analyze the data, is this person blind for the group allocation?
RESPONSE: To describe that the experimenter analyzing the data will be blinded to group allocation the following text has been added under the Analysis heading: “and the experimenter responsible for data analysis will be blinded to group allocation.” (p. 13, line 17-18)

• What is the risk for contamination?
RESPONSE: We acknowledge there is some risk of contamination, but it is minimal. In order to reduce the risk of contamination each participant has unique password to access the online education intervention. In addition, the participant must be enrolled into the program by the experimenter, and is subsequently unenrolled after they have received 4-weeks access. Furthermore, feedback of correct

or incorrect answers for the assessment questions in the knowledge outcome measures are not provided. The following text has been added to address the issue of contamination under the Intervention heading: “To reduce contamination each participant has an individual password to access the online education program, and must be enrolled into the program by the experimenter (and are subsequently unenrolled once they have received 4-weeks access to the program). Furthermore, feedback regarding correct responses to the outcome measures (i.e., the MCQs and case vignettes) is not provided.” (p. 9, line 8-12)

• How is the privacy of participants guaranteed?
RESPONSE: To describe how privacy is maintained the following text has been added under the Recruitment heading: “Upon entering the study, each participant is allocated a participant identification code. To protect the participants’ privacy, the outcome data is kept in a separate password protected file from the document containing the participants’ names and identification codes. All documents related to the study are stored on a restricted access server in password-protected files as per UNSW HREC requirements.” (p. 7, line 24; p. 8, line 1-4)

• Are the outcome measures newly formed questionnaires, or based on validated questionnaires? If the questionnaires are new the validity of the questionnaire can be a serious issue.
RESPONSE: We acknowledge that these measures have not yet been through a comprehensive validation process. The content of the outcome measures has been constructed by an expert research group consisting of physicians, exercise physiologists and clinical psychologists and designed to test a range of knowledge across different professions.

The following text has been added under the Outcomes heading to acknowledge this lack of validation: “These measures have been constructed by an expert research group consisting of physicians, exercise physiologists and clinical psychologists and designed to test knowledge across the range of allied health professions.” (p. 11, line 19-21)

Discussion

The fact that convenience sampling will be used in the study can be a serious threat for further implementation of this intervention. Professionals with an interest in CFS probably will sign up for this intervention, but not professionals who are skeptical towards this group of patients and the diagnosis CFS. This should be acknowledged in the discussion.
RESPONSE: The possibility of convenience sampling has been acknowledged in the discussion: “Given the possibility of convenience sampling of allied health professionals further investigation regarding the efficacy of the intervention on a sample that have yet to formulate opinions regarding intervention for CFS would also be valuable (e.g., implemented within a tertiary allied health training program or mandated for all staff in a health professional service).” (p. 15, line 1-4)

The discussion starts with “the limited understanding of the pathophysiological mechanisms and absence of curative treatments”, while the introduction starts with the benefits of CBT and GET. The authors seem to bring up a new issue here, while it is not previously described. I think the main issue is the limited uptake of CFS management programs, and limited knowledge of health professionals, and that this should be the main issue that the researches will try to improve.
RESPONSE: The initial sentence has been modified to meet this recommendation: “Given the serious and debilitating nature of CFS and the absence of curative treatments, it is unfortunate that there has been limited uptake of evidence-based treatments aimed at managing symptoms and improving patient function” (p. 14, line 6-8)

VERSION 2 – REVIEW

REVIEWER	Robyn Fary

	Curtin University, Australia
REVIEW RETURNED	05-Jan-2017

GENERAL COMMENTS	Thank you for considering and addressing my comments. In general my concerns have been answered satisfactorily. I note that you were unable to find the word "regarding" for correction. It is now located in line 30 on page 6 of the pdf document. Part of the sentence beginning, "While the impact of online educational..." remains confusing. I would have thought that part of that sentence over lines 28-30, page 6 would make more sense if it were worded ".....none, to our knowledge, have investigated the impact OF online educational activities ON CHS management" rather than "..... none, to our knowledge, have investigated the impact ON online educational activities REGARDING CHS management." Please forgive capitals, they are the only format I have available to show the suggested changes. I respect your decision to retain the use of "for example" for some of the references. For consistency please make sure that they are all "for example" or all "e.g." Different formatting is used in lines 25 and 27 on page 6 of the pdf document. The addition of information about the cohort study is welcome. I also note the pragmatic decision not to have another data collection time point after the control group has had access to the intervention, and your clarification of outcome measures. However, the last sentence of the Introduction prior to the Methods and analysis heading states that, "Retention of knowledge, ... will also be assessed in a cohort study design with participants pooled from the intervention and wait-list control groups." While I acknowledge that you have clarified this elsewhere, I would suggest rewording this sentence for consistency clarifying that retention of knowledge is only being assessed in the experimental group. One final comment about the addition of content regarding the cohort study. I am not sure that "success" is the correct term to be used in line 14 on page 7 of the pdf document. The cohort study is stated as assessing, 1) retention of knowledge and self-reported confidence in managing people with CFS amongst the experimental group and 2) satisfaction with the online program and the influence of the education program on clinical practice behaviour in both the experimental and control groups. I do not think that these outcomes readily relate to "....changes in self-reported success in treating people with CFS..."

REVIEWER	Dr. Keith J. Geraghty Centre for Primary Care University of Manchester UK
REVIEW RETURNED	22-Dec-2016

GENERAL COMMENTS	Thank you for opportunity to review this paper following the authors edits. I have given the resubmitted paper fair attention. Overall, I am happy that the authors have responded to the comments of the reviewers; there was some consistency across all

	three reviews. I have paid particularly attention to issues surrounding the design of the trial and the strength of the evidence for the efficacy claims by the authors (in relation to published evidence) of CBT and GET as interventions for CFS. I am not satisfied the authors have fully understood this evidence (it is ok to say there is evidence of benefit - but this really needs to be qualified). It is ok to say there are meta-studies that find benefits, but the picture is a good bit more mixed/nuanced than the authors make out. For instance, there is little evidence for long term benefits or for restoring physical function in ME/CFS. In addition, the largest ever RCT of these treatments (the PACE trial) has come under serious scrutiny and has attracted criticism for its efficacy claims. The PACE team claimed 22% recovery using CBT and GET for CFS, yet a recent published paper puts this at near 7%, with standard care at 4% - leaving only a 3% added value. A Cochrane review by Price et al only offers a 14% added value. This would equate to just 1-2 in 10 patients finding benefit from CBT and GET. (what of the other 8-9 patients?) The authors of the proposed RCT do not paint this picture - they just state there is good level 1 evidence for benefit (as their trial rests on this evidence). They are not giving the reader, or indeed the allied health professionals they will recruit, a fair appraisal of the evidence. This may be highly misleading and a major design bias within this trial. Essentially the authors project claims of strong clear benefits (without really discussing what the term 'benefit' means); then they have developed an education programme based on CBT and GET that they will administer to allied health professionals (we don't know too much about which ones, their training and so on); and it is just assumed in a way, that this programme will benefit the professionals, and the authors will gauge their knowledge of managing CFS patients. * I have added details about evidence in the attached paper/ this should be included in your own paper to some degree i.e. be acknowledged I have some concerns for the safety and well-being of patients participating in this trial (via their interactions with the allied health professionals). The authors state that CBT and GET are beneficial interventions for CFS without giving more detail about the types of patients that benefit, how they benefit, what happens to those patients that don't benefit, or refuse to take part in CBT-GET (this is almost totally ignored - yet should be part of any training for health professionals). The authors need to consider these points to safeguard patients. I also have concerns that the authors expect far too much from the AHPs – i.e. should an OT be expected to assess mental health status, identify depression or anxiety and refer on?, should a physio be expected to also be a competent CBT therapist after a couple of weeks online education programme? – I am very doubtful of this, and the risks to patients are clear, HPAs with only cursory knowledge of ME/CFS being asked to 'manage' ME/CFS patients with complex needs. The authors must remove many terms (or indeed, teaching materials) that talk about managing these patients; this should be the responsibility of a primary physician/care giver, with the HPA acting in a support role. This is not articulated claerly within this RCT. HPAs should be given as much advice on why patients with ME/CFS may not respond well to CBT-GET, as advice on how it benefits – unless the authors want to run trial with strong expectancy and placebo running throughout. I understand the time and effort that goes into developing an RCT and implementing it in practice. I trust my comments might assist the authors in developing a more robust trial/study.

	The reviewer also provided a file in addition to this comment. Please contact the publisher for full details.

REVIEWER	Dr. Martine Goedendorp Department of Health Psychology, University Medical Center Groningen, The Netherlands
REVIEW RETURNED	03-Jan-2017

GENERAL COMMENTS	Thank you for giving me the opportunity to reread the manuscript and evaluate the responses of the authors on my comments. The authors responded well and accurately to the comments and the manuscript has been adjusted accordingly. I do have a few minor comments. Minor revisions: • I still have my concerns about the risk of contamination. Although the participants receive an individual password to access the online education program, will participants be told that they cannot share the password with someone else, or will participants be asked after the course if they shared the password with someone else (a colleague for example)? The latter way might be an indication if contamination occurred. • At the end of the final paragraph of the introduction a full stop is missing. • Sometimes there is, and sometimes there isn't a space before the square brackets of the references. This should be corrected consistently.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Robyn Fary
Institution and Country: Curtin University, Australia Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below Thank you for considering and addressing my comments. In general my concerns have been answered satisfactorily.

I note that you were unable to find the word "regarding" for correction. It is now located in line 30 on page 6 of the pdf document. Part of the sentence beginning, "While the impact of online educational..." remains confusing. I would have thought that part of that sentence over lines 28-30, page 6 would make more sense if it were worded ".....none, to our knowledge, have investigated the impact OF online educational activities ON CHS management" rather than "..... none, to our knowledge, have investigated the impact ON online educational activities REGARDING CHS management." Please forgive capitals, they are the only format I have available to show the suggested changes.
RESPONSE: Thank you for clarifying this suggestion. The sentence has been reworded as suggested (page 6, line 16).

I respect your decision to retain the use of "for example" for some of the references. For consistency please make sure that they are all "for example" or all "e.g." Different formatting is used in lines 25 and 27 on page 6 of the pdf document.
RESPONSE: "e.g.," has been changed to "for example" (page 6, line 15).

The addition of information about the cohort study is welcome. I also note the pragmatic decision not to have another data collection time point after the control group has had access to the intervention, and your clarification of outcome measures. However, the last sentence of the Introduction prior to the Methods and analysis heading states that, "Retention of knowledge, ... will also be assessed in a cohort study design with participants pooled from the intervention and wait-list control groups." While I acknowledge that you have clarified this elsewhere, I would suggest rewording this sentence for consistency clarifying that retention of knowledge is only being assessed in the experimental group.
RESPONSE: The sentence "Retention of knowledge, ... will also be assessed in a cohort study design with participants pooled from the intervention and wait-list control groups." has been reworded to: “Satisfaction with the online education program will also be assessed, as will retention of knowledge, for the intervention group only. The influence of the education program on clinical practice behavior will be assessed in a cohort study design with participants pooled from the intervention and wait-list control groups.” (page 6, lines 21-24)

One final comment about the addition of content regarding the cohort study. I am not sure that "success" is the correct term to be used in line 14 on page 7 of the pdf document. The cohort study is stated as assessing, 1) retention of knowledge and self-reported confidence in managing people with CFS amongst the experimental group and 2) satisfaction with the online program and the influence of the education program on clinical practice behaviour in both the experimental and control groups. I do not think that these outcomes readily relate to "....changes in self-reported success in treating people with CFS..."
RESPONSE: In the current, revised version of the manuscript the following variables are listed as secondary outcome measures of the RCT study: retention of knowledge, as well as confidence of participants in their clinical skills, between the post-intervention assessment and follow up for the intervention group only, and adherence to, and satisfaction with, the online education. In the section of the manuscript titled “Cohort study outcomes”, the primary outcomes are listed as: 1) participants' self-reported success in treating people with CFS; and 2) practice behaviours as the portion of clientele who have CFS. We therefore suggest that the use of the term “success” is appropriate in this context, and highlight that participants are explicitly asked to rate their “success” in treating people with CFS.

Reviewer: 2
Reviewer Name: Dr. Keith J. Geraghty
Institution and Country: Centre for Primary Care, University of Manchester, UK Please state any competing interests or state ‘None declared’: none

Please leave your comments for the authors below Thank you for opportunity to review this paper following the authors edits. I have given the resubmitted paper fair attention.

Overall, I am happy that the authors have responded to the comments of the reviewers; there was some consistency across all three reviews. I have paid particularly attention to issues surrounding the design of the trial and the strength of the evidence for the efficacy claims by the authors (in relation to published evidence) of CBT and GET as interventions for CFS. I am not satisfied the authors have fully understood this evidence (it is ok to say there is evidence of benefit - but this really needs to be qualified). It is ok to say there are meta-studies that find benefits, but the picture is a good bit more mixed/nuanced than the authors make out. For instance, there is little evidence for long term benefits or for restoring physical function in ME/CFS. In addition, the largest ever RCT of these treatments (the PACE trial) has come under serious scrutiny and has attracted criticism for its efficacy claims. The PACE team claimed 22% recovery using CBT and GET for CFS, yet a recent published paper puts this at near 7%, with standard care at 4% - leaving only a 3% added value. A Cochrane review by

Price et al only offers a 14% added value. This would equate to just 1-2 in 10 patients finding benefit from CBT and GET. (what of the other 8-9 patients?) The authors of the proposed RCT do not paint this picture - they just state there is good level 1 evidence for benefit (as their trial rests on this evidence). They are not giving the reader, or indeed the allied health professionals they will recruit, a fair appraisal of the evidence. This may be highly misleading and a major design bias within this trial. Essentially the authors project claims of strong clear benefits (without really discussing what the term 'benefit' means); then they have developed an education programme based on CBT and GET that they will administer to allied health professionals (we don't know too much about which ones, their training and so on); and it is just assumed in a way, that this programme will benefit the professionals, and the authors will gauge their knowledge of managing CFS patients. * I have added details about evidence in the attached paper/ this should be included in your own paper to some degree i.e. be acknowledged.
RESPONSE: Our interpretation of the literature regarding the efficacy of CBT/GET as an intervention for CFS is that the data demonstrates statistically significant benefit across a number of well controlled studies. To indicate the moderate effect sizes of benefit consistently demonstrated in meta-analyses of these interventions we have added "moderately" to the following sentence: "More than 20 randomised controlled trials by independent researchers examining the effectiveness of CBT or GET across separate patient groups and in various geographical locations have found moderately beneficial effects of these interventions for CFS….." (page 4, line 9)
We acknowledge that, as with many accepted healthcare interventions, the extent to which an individual benefits may vary from negligible to clinically significant. We believe we have addressed this in the following sentence with text added to identify the potential for a biased patient sample in RCT studies: "When applied appropriately the interventions are not associated with harm[4, 7, 8], and the beneficial effects vary in magnitude from negligible to clinically significant [3, 4] (This conclusion relates to patients who are able to attend a clinic and may not generalise to more disabled patients). (page 4, lines 13-16).

The following text has been added to operationalise the term "benefit": "More than 20 randomised controlled trials by independent researchers examining the effectiveness of CBT or GET across separate patient groups and in various geographical locations have found moderately beneficial effects of these interventions for CFS, including significantly reduced levels of fatigue, functional impairment, depression and anxiety, in group-wise outcome analyses (for a review see[5])." (page 4, lines 10-11)
We also wish to point out that the education intervention includes an initial section on "Fatigue assessment tools" to ensure that clinicians are aware of suitable outcome measures to gauge the response of individual patients, and patient groups, to intervention.

I have some concerns for the safety and well-being of patients participating in this trial (via their interactions with the allied health professionals). The authors state that CBT and GET are beneficial interventions for CFS without giving more detail about the types of patients that benefit, how they benefit, what happens to those patients that don't benefit, or refuse to take part in CBT-GET (this is almost totally ignored - yet should be part of any training for health professionals). The authors need to consider these points to safeguard patients. I also have concerns that the authors expect far too much from the AHPs – i.e. should an OT be expected to assess mental health status, identify depression or anxiety and refer on?, should a physio be expected to also be a competent CBT therapist after a couple of weeks online education programme? – I am very doubtful of this, and the risks to patients are clear, HPAs with only cursory knowledge of ME/CFS being asked to 'manage' ME/CFS patients with complex needs. The authors must remove many terms (or indeed, teaching materials) that talk about managing these patients; this should be the responsibility of a primary physician/care giver, with the HPA acting in a support role. This is not articulated claerly within this RCT. HPAs should be given as much advice on why patients with ME/CFS may not respond well to CBT-GET, as advice on how it benefits – unless the authors want to run trial with strong expectancy

and placebo running throughout.
RESPONSE: The reviewer misinterprets the subject group being recruited as including patients. This trial recruits allied health professionals only. It is an evaluation of an online education program to improve allied health professionals' knowledge and confidence to treat CFS.

Regarding our expectations of the capacity of allied health professionals to provide evidence-based interventions for CFS - as mentioned in our previous response to this comment in the initial review - in Australasia, Europe, and the USA, after suitable training CBT interventions can be, and are, provided by several different allied health professionals. We acknowledge that at times the application of CBT is in the absence of appropriate expertise. The goal of the online education program, indeed its very purpose, is to evaluate whether an online education activity for allied health professionals is effective in imparting the knowledge required to develop expertise in providing interventions for CFS. Again, as previously mentioned, part of this training is to identify when further expertise is required and when a multi-disciplinary or inter-disciplinary approach is necessary. We remind the reviewer again that this is an evaluation of an education activity to improve knowledge of CFS and confidence to treat patients with CFS. An evaluation of practice behaviours (apart from the portion of the participants' clientele with CFS) and patient outcomes resulting from the education activity is beyond the scope of this study.
I understand the time and effort that goes into developing an RCT and implementing it in practice. I trust my comments might assist the authors in developing a more robust trial/study.

Reviewer: 3
Reviewer Name: Dr. Martine Goedendorp
Institution and Country: Department of Health Psychology, University Medical Center Groningen, The Netherlands Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below Thank you for giving me the opportunity to reread the manuscript and evaluate the responses of the authors on my comments. The authors responded well and accurately to the comments and the manuscript has been adjusted accordingly. I do have a few minor comments.

Minor revisions:
• I still have my concerns about the risk of contamination. Although the participants receive an individual password to access the online education program, will participants be told that they cannot share the password with someone else, or will participants be asked after the course if they shared the password with someone else (a colleague for example)? The latter way might be an indication if contamination occurred.
RESPONSE: In addition to an individual password the participant must also be enrolled into the study by the experimenter to gain access to the online education activity. After 4-weeks access they are unenrolled and unable to gain further access. This tight control of access to the intervention should help to prevent contamination. However, as suggested, upon receiving the password, participants will be explicitly instructed not to share their password. We decided against the inclusion of a question asking the participant if they had shared their password as we did not think this would necessarily prompt an honest response and would not be a valid representation of contamination. Because access is provided at no cost to participants the incentive for any sharing of password access is very low. Even if it did occur the effect would be to reduce group differences on the outcome measures rather than leading to a false positive finding.

The following text has been added:
"To reduce contamination each participant has an individual password to access the online education program and are asked not to share this access by providing their password to others," (page 9, Lines 9-10).

• At the end of the final paragraph of the introduction a full stop is missing.
RESPONSE: Full stop added.

• Sometimes there is, and sometimes there isn't a space before the square brackets of the references. This should be corrected consistently.
RESPONSE: The space between the square brackets and text has been deleted, as per BMJ Open guidelines.

VERSION 3 – REVIEW

REVIEWER	Robyn Fary Curtin University, Australia
REVIEW RETURNED	09-Feb-2017

GENERAL COMMENTS	The responses to my latest comments have been made satisfactorily.

REVIEWER	Dr. Keith J. Geraghty University of Manchester Institute of Population Health
REVIEW RETURNED	20-Jan-2017

GENERAL COMMENTS	It is always interesting when the authors of a paper respond to tell the reviewer that the reviewer has misinterpreted their paper/study. Let me be crystal clear that I am fully aware that your RCT does not recruit patients, but it does recruit allied health professionals (AHPs); and it attempts to educate them in how to treat 'patients' with CFS, 'manage' patients with CFS, and it will explore their knowledge and confidence in dealing with 'patients' with CFS. My advice to the authors, if you are going to accuse the reviewer of not understanding your study, do make sure you've understood the reviewers comments! Let's look at your language; something I pointed out in the first review: do allied health professionals 'treat' CFS? You use the word 'treat'. To me this means offers a treatment. Could you explain to me how an occupational therapist treats CFS, and psychiatric co-morbidity, pain, sleep disturbances and any other symptom that might crop up related to the patients' condition? Please use appropriate terminology – I would assume some of the AHP will administer some therapies such as CBT and GET. My other comment was, are AHPs equipped enough to treat and manage CFS based on a short-online education programme (based on your highly biased interpretation of what works as a treatment). Above you argued with me that CBT is an effective therapy. Just today I was reviewing the results of the FINE trial, a trial of home-based CBT-GET for CFS in the UK, published in the BMJ. At 70 weeks evaluation FINE found no benefits across a range of subscales of quality of life and physical function following CBT (or pragmatic rehabilitation) (Wearden et al. 2010). I assume many of your AHPs might offer home-based CBT? If so, the evidence base doesn't exist. The 20 or so RCTs you base your efficacy claims on do not provide strong robust evidence of benefit. Only very recently, Wiltshire et al. published a paper on the recovery rates found in the PACE trial (2016, Jr of Fatigue and Biomedicine) showing how there was insignificant to no added benefit using CBT or GET over usual care. This is the largest ever conducted RCT or CBT for CFS. The

	authors own recovery paper shows a similar finding that the benefits of CBT between groups fell away at 2.5 years follow-up (Sharpe et al); a finding flagged by Price et al in their Cochrane Review. So what we end up with is a small to modest benefit, for mild cases, with no long term benefit, no theoretical basis for treatment proven, and no evidence of CBT being physically restorative – and yet you want to run an RCT showing AHPs how good CBT is and then you want them to use it and after this you will assess their knowledge and perceptions of CBT. There is nothing further I can add to this review. I appreciate that the authors have amended their paper slightly in response to my previous review comments. I will reluctantly accept this paper for publication, however I stand over my concerns about strong design biases, strong researcher bias, and the potential for patient harm if AHPs are attempting to treat CFS with little expertise of the condition. At best, AHPs can provide adjunct support to CFS patients – I feel the aim of this quasi-RCT is to indoctrinate AHPs about the benefits of CBT with some motive to promote CBT as an effective treatment for CFS – when the evidence does not support this claim. There are clear risks for the health professionals being recruited and the patients they will subsequently treat. The authors state “The goal of the online education program, indeed its very purpose, is to evaluate whether an online education activity for allied health professionals is effective in imparting the knowledge required to develop expertise in providing interventions for CFS.” As per my last review submission, a short online course on CFS will not impart expertise to the allied health professional and they should not be expected to treat CFS as experts. My view is that AHP should work with clinical experts in CFS to offer a range of psychological and social support to CFS sufferers – not just CBT, as dictated by this RCT.

REVIEWER	Martine M. Goedendorp University Medical Center Groningen, University of Groningen, Groningen
REVIEW RETURNED	31-Jan-2017

GENERAL COMMENTS	Thank you for giving me the opportunity to reread the manuscript and evaluate the responses of the authors on my comments. The authors responded well and accurately to the comments and the manuscript has been adjusted accordingly. I still have my concerns about the risk of contamination, especially when colleagues are assigned to different trial conditions. Although participants are told that they shouldn’t share the password with someone else, which is an important aspect, if information is shared by participants of the intervention group to participants of the control group contamination is a risk.

VERSION 3 – AUTHOR RESPONSE

Reviewer: 2

Reviewer Name
Dr. Keith J. Geraghty

Institution and Country
University of Manchester
Institute of Population Health

Please state any competing interests or state ‘None declared’:
none

Please leave your comments for the authors below
COMMENT: It is always interesting when the authors of a paper respond to tell the reviewer that the reviewer has misinterpreted their paper/study. Let me be crystal clear that I am fully aware that your RCT does not recruit patients, but it does recruit allied health professionals (AHPs); and it attempts to educate them in how to treat ‘patients’ with CFS, ‘manage’ patients with CFS, and it will explore their knowledge and confidence in dealing with ‘patients’ with CFS. My advice to the authors, if you are going to accuse the reviewer of not understanding your study, do make sure you’ve understood the reviewers comments!
Let’s look at your language; something I pointed out in the first review: do allied health professionals 'treat' CFS? You use the word ‘treat’. To me this means offers a treatment. Could you explain to me how an occupational therapist treats CFS, and psychiatric co-morbidity, pain, sleep disturbances and any other symptom that might crop up related to the patients’ condition? Please use appropriate terminology – I would assume some of the AHP will administer some therapies such as CBT and GET.

RESPONSE: We regard this comment with incredulity – allied health professional of all sorts will treat patients with CFS by applying the elements of CBT or GET following the training. Reviewer 2 seems to imply that occupational therapists are incapable of advising patients on GET, which is essentially an insult to that profession whose primary focus is on rehabilitation of those with disability.
The role of allied health professionals in multidisciplinary care is widely recognised for many chronic conditions. Part of educating health professionals in multidisciplinary care is to improve their understanding of the role and approaches used by other health professionals. Hence, all participants in the trial will learn about the breadth of the CBT and GET intervention, even though their practice might involve only a component of the intervention delivered in conjunction with other health professionals. Again, our study will test what knowledge and skills are developed after the online learning intervention.

As the word ‘treatment’ has no intrinsic implication of curative intent, we regard this reviewer’s premise as flawed. Nevertheless, the word ‘treat’ or ‘treatment’ has been changed to ‘the management of’ or ‘intervention’ throughout the manuscript - simply for consistency.

COMMENT: My other comment was, are AHPs equipped enough to treat and manage CFS based on a short-online education programme (based on your highly biased interpretation of what works as a treatment). Above you argued with me that CBT is an effective therapy. Just today I was reviewing the results of the FINE trial, a trial of home-based CBT-GET for CFS in the UK, published in the BMJ. At 70 weeks evaluation FINE found no benefits across a range of subscales of quality of life and physical function following CBT (or pragmatic rehabilitation) (Wearden et al. 2010). I assume many of your AHPs might offer home-based CBT? If so, the evidence base doesn’t exist. The 20 or so RCTs you base your efficacy claims on do not provide strong robust evidence of benefit. Only very recently, Wiltshire et al. published a paper on the recovery rates found in the PACE trial (2016, Jr of Fatigue and Biomedicine) showing how there was insignificant to no added benefit using CBT or GET over usual care. This is the largest ever conducted RCT or CBT for CFS. The authors own recovery paper

shows a similar finding that the benefits of CBT between groups fell away at 2.5 years follow-up (Sharpe et al); a finding flagged by Price et al in their Cochrane Review. So what we end up with is a small to modest benefit, for mild cases, with no long term benefit, no theoretical basis for treatment proven, and no evidence of CBT being physically restorative – and yet you want to run an RCT showing AHPs how good CBT is and then you want them to use it and after this you will assess their knowledge and perceptions of CBT.

RESPONSE: We have already engaged in considerable to and fro regarding the efficacy of CBT and GET for CFS, and have modified the manuscript to acknowledge the limitations of the Level One evidence. If this reviewer is now seeking in this comment to suggest that CBT should be regarded as ineffective as one new study showed non-sustained benefit after six years when any number of secondary factors (sleep disorder, mood disorder, intercurrent illness) are likely to have come in to play, we regard that as simply inadequate scientific consideration of the topic. Of course, initial benefits from CBT may require repeated or longer term interventions to sustain positive outcomes – that issue is entirely irrelevant to the topic of this manuscript.

COMMENT: There is nothing further I can add to this review. I appreciate that the authors have amended their paper slightly in response to my previous review comments. I will reluctantly accept this paper for publication, however I stand over my concerns about strong design biases, strong researcher bias, and the potential for patient harm if AHPs are attempting to treat CFS with little expertise of the condition.

RESPONSE: We reject this reviewer's assertions of "strong design biases, strong researcher bias" – either the manuscript completes scientific peer review and is found to present a balanced appraisal of the literature and a robust study design – or not. It would seem the other reviewers are of the former opinion.
The "potential for patient harm if AHPs are attempting to treat CFS with little expertise of the condition" is nonsense as it is exactly the rationale of the study.

COMMENT: At best, AHPs can provide adjunct support to CFS patients – I feel the aim of this quasi-RCT is to indoctrinate AHPs about the benefits of CBT with some motive to promote CBT as an effective treatment for CFS – when the evidence does not support this claim. There are clear risks for the health professionals being recruited and the patients they will subsequently treat.

RESPONSE: We regard this comment also with incredulity. Can the Journal really regard this individual as a balanced scientific reviewer when he refers to a carefully considered clinical trial protocol of an education intervention as "indoctrination"?
The notion of "clear risks for the health professionals being recruited" is surely humorous – as if health professionals are incapable of making judgements about how they spend their time in training, and in which patients they opt to treat and how they do so.

COMMENT: The authors state "The goal of the online education program, indeed its very purpose, is to evaluate whether an online education activity for allied health professionals is effective in imparting the knowledge required to develop expertise in providing interventions for CFS." As per my last review submission, a short online course on CFS will not impart expertise to the allied health professional and they should not be expected to treat CFS as experts. My view is that AHP should work with clinical experts in CFS to offer a range of psychological and social support to CFS sufferers – not just CBT, as dictated by this RCT.

RESPONSE: We agree with the reviewer that: "AHP should work with clinical experts in CFS to offer a range of psychological and social support to CFS sufferers – not just CBT ". This is the model followed in our own clinic, whereby there is close liaison with medical practitioners and the module-

based program on which the education intervention is based, and includes a range of psychological support, as well as GET, in addition to CBT. It is not just CBT.

With regard to the reviewer's concern with the knowledge that may be imparted via an online intervention, the trial specifically aims to test what knowledge and skills are imparted. We do not anticipate participants will be 'expert' simply after completion of the trial but have aimed to test the hypothesis that the intervention provides the knowledge required to develop expertise.

RESPONSE:

Reviewer: 3

Reviewer Name
Martine M. Goedendorp

Institution and Country
University Medical Center Groningen, University of Groningen, Groningen

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
COMMENT: Thank you for giving me the opportunity to reread the manuscript and evaluate the responses of the authors on my comments. The authors responded well and accurately to the comments and the manuscript has been adjusted accordingly. I still have my concerns about the risk of contamination, especially when colleagues are assigned to different trial conditions. Although participants are told that they shouldn't share the password with someone else, which is an important aspect, if information is shared by participants of the intervention group to participants of the control group contamination is a risk.

RESPONSE: We do appreciate that we are unable to completely eliminate the potential for contamination in a trial such as this, i.e., that delivers the intervention in an online format. Any contamination, however, will most likely act to reduce group differences and therefore not result in an erroneous rejection of the null hypothesis. In reporting the outcome of the trial we will acknowledge this potential influence to underestimate the effect of the online education intervention.

Reviewer: 1

Reviewer Name
Robyn Fary

Institution and Country
Curtin University, Australia

Please state any competing interests or state 'None declared':
None declared

Please leave your comments for the authors below
The responses to my latest comments have been made satisfactorily.

VERSION 4 – REVIEW

REVIEWER	Dr. Keith J. Geraghty Division of Health Sciences Primary Care University of Manchester
REVIEW RETURNED	09-Mar-2017

GENERAL COMMENTS	I have written to the Editor to ask them to reprimand you for attempting to tarnish the credibility of a reviewer in this process (myself being that reviewer). I want to remind you that I "accepted" your article for publication after the second round, thus I find your remarks unprofessional and distasteful. I wrote in my previous review to you "There is nothing further I can add to this review. I appreciate that the authors have amended their paper slightly in response to my previous review comments. I will reluctantly accept this paper for publication". This is how professionals should behave (reviewers and authors), we review papers on their merits, freeing ourselves of bias as much as is humanly possible. For your information I am not a "patient advocate". I belong to no patient organisation, I represent no patient organisations, I speak for no patient or patient group – thus your claim is unsubstantiated. You are right that I have suffered from CFS, my own condition started whilst a medical student, I have made a strong recovery. I began doing work in ME/CFS five years ago. I took an honorary position at the University of Manchester as this allowed me manage studying for professional exams (Faculty of Public Health) and other things. I have since been employed by the University of Manchester to work on physician burnout. I have published 6 papers in 2016, a paper on burnout published in the American Medical Journal and five papers published on ME/CFS. I have read over 1000 papers and vast sways of literature in this field – I consider myself an expert. I hold five degrees including a master of public health and a PhD in health services research. I have three papers in submission on ME/CFS in 2017, including original research. I have a masters in research methodology and a keen interest in evidenced-based medicine and clinical trials, thus I feel uniquely qualified to review your paper. I will point out to you that in the first round all three independent reviewers called for corrections and resubmission. I have been offered a prestigious post-doctoral fellowship to undertake quite new and innovative experiments in ME/CFS neuroscience at another UK University – I have accepted and all being well I being in the summer. Your paper has been reviewed fairly, I would urge you not to try to denigrate the professionalism and integrity of the reviewer in future – you should spend more time and energy on responding to reviewers' questions that attempting to bypass the review process by questioning the reviewer's status as expert. I will not offer any further comment on your paper – I previously accepted it for publication but I hold up my right to question the potential for patient harm in your RCT, safeguarding patients and health professionals is more important that your views of me. I stand over my comments that you may cause harm to both patients with CFS and allied health professionals by offering them a short

	online course on CFS, not explaining the context of the AHPs role in how they will use their knowledge, not outlining risks to patients or AHPs, not being aware of the literature and presenting it farily (eg the efficacy of CBT for CFS - you may want to read my paper on this Geraghty and Blease in Jr of Health Psychology). You must learn to take reviewers comments on board and to view them as constructive comments that will help you develop more reliable and robust studies. I have nothing further to add.